Thacher (J. S.)

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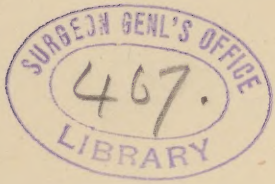
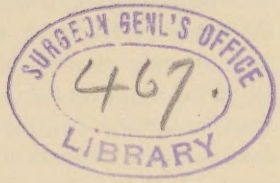


Reprinted from the New York Medical Journal for April 2, 1892.



THE DIAGNOSIS OF PANCREATIC DISEASE.*

By JOHN S. THACHER, M. D.

The unsatisfactory position which the pancreas holds in the minds of clinicians is indicated by the scant attention which the best modern works on clinical medicine give to the consideration of its diseases. Fagge's book does not discuss the subject at all. Strümpell gives thirty lines to the symptoms and diagnosis of the various diseases of the pancreas, and Flint gives fifty. Briscoe, in one of the most recent English text-books on medicine, says that "very little of clinical value is known about the diseases of the pancreas, and it would be a waste of time to discuss their diagnosis." Friedreich, in von Ziemssen, says that "the pancreas does not possess any function the suppression of which would produce appreciable symptoms." This being the position of the best representatives of the profession even up to quite recent times, while indicating a conspicuous need, it would discourage us from any attempt to clear up our ignorance in this direction, were it not that several interest-

* Read before the Hospital Graduates' Club, at its fifty-fourth meeting, November 19, 1891.

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ing observations have recently been made bearing upon the subject.

The pancreatic functions which are best understood are the digestive functions, and indeed until very lately these were the only ones which it had been even suspected of. Of all the digestive fluids the pancreatic juice is the most important, doing a greater work upon a greater variety of food elements than any of the other fluids of the alimentary canal. It would seem, then, that any disease of this organ, interfering with the production of this juice, would promptly and conspicuously manifest itself, and we would expect to find proteids, starches, and fats appearing undigested in the fæces, and the patient's general nutrition distinctly interfered with. But both clinical and experimental observations on this point disappoint our *a priori* expectations. As regards starch, while Abelmann's studies upon a dog whose pancreas had been removed indicate a marked diminution in the digestion and absorption of starch, yet there are enough cases pointing otherwise to make Leo briefly dismiss the subject with the words that "the digestion of starch is in no way affected by the absence of pancreatic juice."

As regards proteids, there have been some experiments and some clinical observations showing that a pancreatic lesion may lead to the presence of abundant meat fibers in the fæces. But the experiments of Müller and clinical experience seem to teach us that Leo is right in saying that "the effect on the digestion of meat is not sufficiently marked and constant to be of any value for the diagnosis of pancreatic disease." In the fats we have something to which most clinicians have pinned their faith as about the only reliable indication for the diagnosis of these diseases, and it can not be denied that in several cases an abundance of fat has been passed from the rectum, and certain experiments, notably

those of Abelmann, point in the same direction; but the basis of the belief in this diagnostic point has, on further observation, become much weakened. As Leube states, "an unusual abundance of fat in the fæces, which one would expect in all diseases of the pancreas, and especially in total degeneration of the gland, is usually not found." Or, as Leo puts it, "it has been shown that the view often heretofore expressed, that an absence of the pancreatic juice from the alimentary canal produces an abundant presence of fat in the fæces, is incorrect."

There have lately appeared the detailed reports of several interesting experimental observations upon the absorption of fats from the alimentary canal, and the influence upon this of the pancreatic juice and the bile, with quite uniform testimony to the predominating influence of the bile, leading us to an opinion that if there be simply an absence of the pancreatic juice from the intestines, while the bile is normal, the absorption of fats will ordinarily be complete.

The experiments of Müller show that where the bile is cut off from the intestines, while the absorption of starch and proteids is very little or not at all affected, the absorption of fat falls from about ninety per cent. to between forty-five and twenty per cent., and, on the other hand, that in the absence of pancreatic juice the absorption of starch is not affected, the digestion of proteids is a little less complete, and no effect upon the absorption of fat could be established.

Munk's experiments on a dog with biliary fistula show a great diminution in the absorption of fats; and, again, the experiments of Dastre, while showing a slight diminution in the absorption of fat in the absence of pancreatic juice, show a more marked effect in the same direction from the absence of the bile. Moreover, in none of the cases of

pancreatic cyst collected by Treves did fatty dejecta occur, and according to Grandmaison they are observed more often in cancer, which is generally close to if not involving the duodenum, than in other pancreatic disease. Taking these facts into consideration, and also the fact that lesions of the pancreas are often associated with obstruction of the biliary duct, it seems possible that in many of the cases where fatty dejecta have occurred, they may have been due to shutting off of the bile rather than to the absence of pancreatic juice.

Our practical clinical conclusion, then, as regards the presence of proteids, starch, or fat in the fæces as a basis of diagnosis, must be, that while they may occasionally occur in cases of pancreatic trouble, and when occurring in abundance would be one factor in the diagnosis, yet they usually do not occur, their absence does not by any means indicate a normal condition of the pancreas, and the presence of fat would point more strongly to some trouble of the liver or its ducts.

One point, however, associated with this, is perhaps on its way toward establishment, and that concerns the diminished ratio of the fatty acids to the neutral fats. Müller has shown, from three cases, that the ratio is in diseases of the pancreas diminished from the normal eighty-four per cent. to forty per cent., and Leo says that "the saponifying power of the pancreatic juice is distinctly affected, which gives us the only means of positive proof that the pancreatic juice is not doing its part in the intestinal digestion." This point, however, loses largely from its practical value because of the necessity of elaborate quantitative tests which could not be undertaken except by an experienced chemist.

A further practical point has recently been suggested, and possibly further observations will show it to be well taken. Walker maintains that the presence of the pancre-

atic juice is necessary to the normal pigmentation of the fæces, and that the absence of this juice, as well as the absence of the bile, may produce clay-colored stools.

This is based on two cases. In the first case the patient had light-colored stools without jaundice, the liver on autopsy being normal and the ducts pervious. But there were epigastric pain and diabetes, there were fatty fæces, and at the autopsy the pancreas was found much enlarged, fatty, and fibrous. In the second case the patient had had stone-colored stools, without jaundice or other symptoms of liver trouble, it and its ducts being normal at the autopsy; but there were greasy dejecta, also glycosuria, and at the autopsy the duct of Wirsung was found involved in the cicatrix of an ulcer.

The point suggested to Walker by these cases he also supports by certain further considerations. In the first place, the coloring matter of the bile is not the same as that of the fæces, and is therefore altered chemically by some agent, possibly by the pancreatic juice.

Again, as Claude Bernard observed some thirty-five years ago, "the bile only colors matters a very light yellow, while with the pancreatic juice the bile takes a decided brown tint."

Again, meconium, which contains bile, does not, however, show the usual fæcal color, and it is known that the pancreatic juice does not flow until after birth.

And again, certain drugs which increase the fæcal pigmentation and relieve symptoms of indigestion, are shown by experiments not to increase the secretion of bile.

While these cases and arguments of Walker's can hardly by themselves force us to accept the suggestion based upon them as proved, it seems to be sufficiently worthy of consideration to be borne in mind in suspected cases for further demonstration or disapproval.

Before leaving this discussion of diagnostic aids based on the digestive functions of this gland, let us notice this further point which has been made by Pisenti.

The pancreatic juice effects the change of proteids into peptones, and of these into leucine and tyrosine, from which, by decomposition, are produced skatol, phenol, and especially indol, which latter is in turn the source of indican. From this it would follow that pancreatic disease would lead to the diminution of indican in the urine.

Pisenti's experiments show that ligation of the pancreatic duct reduces the indican of the urine to a quarter of its normal quantity; but, as Leube states, "since human urine in normal condition contains so scant an amount of indican, its absence from the urine or its presence in traces is only of diagnostic value in cases where, from the nature of the attack, an increase of the indican in the urine was to be confidently expected"; or, as Leo puts it, "since tumors of the stomach and intestines are generally accompanied by a marked increase of indican, an epigastric tumor is probably pancreatic if the indican is not increased or is diminished."

Lipuria has been mentioned as a symptom of diseases of the pancreas, but this is certainly so rare as not to merit our attention.

Until quite recent times, experiments have revealed no further functions of the pancreas than the digestive ones; but during the few years just past both experimental and pathological observations have been rapidly accumulating which now oblige us to admit at least the very plausible showing in favor of a further and important office for this gland.

It is true that even in the last century the coincidence of diabetes with pancreatic affections was noted. But Bouchardat was the first to propound a theory of the pancreatic

origin of diabetes. Lanceraux, later, supported this position vigorously. But it was not until the experiments of Mering and Minkowski, reported in 1889, showed that total extirpation of the pancreas was followed by all the characteristic symptoms of diabetes, that the idea of an essential connection between this organ and this disease began to be generally and seriously entertained.

Of twenty-one dogs upon which they operated, three died within twenty-four hours without urinating; the other eighteen all excreted sugar, and the condition after complete removal of the pancreas was "not a simple temporary glycosuria, but a genuine diabetes mellitus, resembling in all respects the most severe forms of this disease in man, even to extreme hunger and thirst, marked polyuria, emaciation, and weakness."

Lépine also extirpated the pancreas from several dogs, and found that in all those in which the autopsy showed complete removal there was marked and increasing glycosuria.

Dominicis has done thirty-four extirpations with less constant results, and yet, of these thirty-four animals, twenty-one had glycosuria, and all showed progressive emaciation, polyuria, polydipsia, and polyphagia, with various affections of the skin.

Remond's experiments included total and partial extirpation and ligature of the excretory ducts, and in each set he sometimes obtained and sometimes failed to obtain glycosuria.

Hedon has operated on twenty-three animals. The first ten died promptly, but improved technique resulted in the survival of the other thirteen, and they all passed glucose in their urine.

Arthaud and Butte also report similar results. They say: "We have repeated the experiment of total removal

of the pancreas, and we have obtained results absolutely identical with those reported by Minkowski and von Mering and afterward by Lépine."

Renzi and Reale reported to the Tenth International Congress that in their experiments total removal of the pancreas was followed, in seventy-five per cent. of the cases, by glycosuria, and made the further interesting announcement that diabetes could be experimentally produced by removal of the duodenum or of the salivary glands.

It is of interest that incomplete extirpations have often failed to produce glycosuria, a remnant of little more than one tenth of the gland being enough in some cases to avoid this result, recalling analogous experiences with myxœdema after thyreoidectomy.

The experiments which we have just reviewed conflict, it is true, with many former experiments on the pancreas, but they were largely ligations of the ducts, and the attempted extirpations were many, possibly most of them, incomplete. If, for instance, we look over Martinotti's reports of the operations from which he drew his decidedly negative conclusions, we find that remnants of the organs were revealed in three of the four cases, and that in the fourth, where none was left, no examination of the urine is reported, but there was marked emaciation.

Klebs and Munk failed to obtain diabetes by ligature or exsection, and referred the diabetes observed by others to lesions of the solar plexus. But Klebs has since expressed his adherence to the pancreatic explanation; and, moreover, Peiper's cases of solar-plexus extirpation from fifteen animals, of which eleven survived, showed no diabetes.

Experimental observations are then very emphatic in support of the causative relation of pancreatic lesions to diabetes.

Nor are post-mortem observations silent on this question. Saundby's carefully detailed reports of the changes in the various organs of fifteen cases of diabetes in man which came to autopsy, show that the most constant and marked was an atrophy of the pancreas, being present in seven of the fifteen, and in all of the typical wasting cases. In four others the gland was firm and fibroid, and in only four did it appear normal.

Baumel professes to have found either gross or microscopic lesions in all the cases of diabetes which he has investigated. And Lanceraux reports twenty consecutive cases of the severe wasting variety, his "*diabète maigre*," which have come under his observation. Of these, fourteen have died, and they have all shown abnormal conditions, obstruction of the ducts, sclerosis, or steatosis. Frerichs reports thirty cases, of which twelve showed an abnormal atrophy. Senator says that one half show pancreatic lesions; and various others have recorded isolated cases illustrating the relation.

My own experience regarding this question has been this: During my connection with the Presbyterian and St. Luke's Hospitals, five autopsies have been made in those institutions upon well-marked cases of diabetes. To these I will add a case from Dr. Draper's practice, in which I examined the organs, and a case in which the autopsy was made by my associate, Dr. Tuttle. These include all the cases clearly of this nature which have during this period come to autopsy within the range of my direct investigation, and in all seven distinct pathological conditions of the pancreas were found.

One was of about one third the normal size, with a flabby atrophied appearance on gross examination. Another was so atrophied that only minute traces of the glandular tissue could be found. Another was of about two thirds the nor-

mal size, with apparently an increase in the interlobular connective tissue. Another was of about half the normal size, firm, and containing hardly any gland tissue except in the head, the rest being only dense connective tissue. Microscopical examination showed an extreme increase in the connective tissue at the expense of gland tissue, a good deal of proliferative endarteritis, and in places large numbers of infiltrated leucocytes. Another was a little larger than the usual size of a pancreas, but, on microscopical examination, showed a distinct, though not very abundant, increase of connective tissue, considerable degeneration of the gland cells, and a marked invasion of the gland by adipose tissue. Another, while not appearing small on gross examination, showed under the microscope extreme invasion by adipose and much increase of connective tissue, while the last case had dilated ducts which contained numerous calculi, the tissues being cirrhotic and atrophied.

In two cases not included in this group the patients were under observation for only six and twenty-four hours —one in coma all of the time and the other a considerable part of the time, so that no histories were obtained; but there was sugar in the urine, and yet the pancreas showed in each case but very slight, perhaps I should say doubtful, lesions.

On the other hand, I have examined the pancreas from a large number of miscellaneous cases, and while slight changes of the kinds related above are sometimes met with, still it is rare to find even a trace of any pathological abnormity.

It is true, on the other hand, that very many cases of pancreatic disease show no sugar in the urine. Of Fitz's seventy cases of acute and suppurative pancreatitis and pancreatic hæmorrhage, in only one is sugar reported—a very small proportion, even after allowing for the many

whose urine was probably not examined because of the brevity of the attack or for other reasons.

Treves's collection of pancreatic cysts were accompanied by glycosuria only "sometimes," and it seems to be in but a small minority of cases of cancer of this organ that the symptom is observed.

And yet, considering all the experimental and pathological observations, we seem forced to respect the idea of a causal relation between pancreatic disease and diabetes, and to admit that for diagnostic purposes diabetes is of some value, pointing to be sure rather to chronic pancreatitis, lithiasis, cirrhosis, degeneration, and steatosis, than to tumors or acute lesions.

Of the suggestions offered to explain how the glycosuria follows from the absence of the pancreas, the most interesting, and the most reasonable in the scant light as yet thrown on the subject, is that which supposes a normal glycolytic ferment produced by the pancreas, thrown into the circulation and necessary to the utilization of glucose.

The blood, when no longer supplied with this, would evidently find itself overloaded with sugar, which it could no longer dispose of. The experiments of Lépine and others bearing on this theory make very pleasant reading, but the interesting nature of the recent observations already described have led us far enough in the discussion of the glycosuria symptom.

Pain in the epigastrium is generally present in acute lesions, often severe and of a colicky or neuralgic character. It is sometimes spoken of as cœliac neuralgia. In the case of cysts the pain is usually slight; in cancers, not, as a rule, prominent; in cases of lithiasis or chronic inflammation it is generally absent; and is probably never caused by steatosis or atrophy.

Jaundice is frequently produced by cancer of the pan-

creas, as would be expected from the intimate relation between the common bile duct and the head of the gland, and often helps to locate an epigastric tumor. It is rarely produced by cysts, and not at all by the other pancreatic lesions.

Ascites and enlargement of the spleen are frequently caused by the pressure of a cancer upon the portal vein, but not by a cyst or by other lesions.

It should be borne in mind that hæmorrhages into the intestine and stomach sometimes occur when the pancreas is diseased. It has been recorded in some cases, and I have happened to see two instances of hæmatemesis due to cancer of the head of the pancreas. In each case the tumor had invaded the wall of the duodenum, producing ulceration, from which the hæmorrhages are supposed to have come.

Compression of the abdominal aorta, with or without pulsation, is an occasional symptom of pancreatic tumor.

Compression of a ureter is rare.

The skin is said to be sometimes bronzed; it is occasionally dusky or yellow.

As regards further indigestion symptoms, there may be loss of appetite, nausea, eructations of gas, a sense of fullness in the epigastrium, and diarrhœa or constipation. Mental dullness and depression are common.

In acute lesions, in addition to the severe pains already mentioned, there are apt to be vomiting and collapse, sometimes fever. A slowing of the pulse is sometimes noticed, particularly in cases of hæmorrhage, and in these, too, death usually comes very quickly, often instantaneously.

Physical examination for a pancreatic cancer has failed to find it in about half the cases, though the gland can sometimes be felt even when normal. When found, it is in the epigastrium, at the mid-line or a little to the right of it, and is, as a rule, very slightly or not at all movable.

A cyst occupies the same position, but is often large, may fill the abdomen, and is generally immovable, round, with distinct outline, tense and elastic, but fluctuation can not always be made out. It usually enlarges rapidly, and has been known to discharge itself into the intestine.

The cyst fluid is generally turbid, brownish, odorless, of rather high specific gravity, alkaline or neutral, and contains albumin, but no urea and no bile. It will generally, but not always, emulsify fats and change starch into sugar.